(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 531 901 A2**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **92115154.4**

(22) Date of filing: **02.09.92**

(51) Int. Cl.5: **C07D 487/04**, A61K 31/505, A61K 31/53, A61K 31/415, //(C07D487/04,239:00,231:00), (C07D487/04,235:00,231:00), (C07D487/04,253:00,231:00)

(30) Priority: **09.09.91 GB 9119267**
02.03.92 GB 9204464

(43) Date of publication of application:
17.03.93 Bulletin 93/11

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

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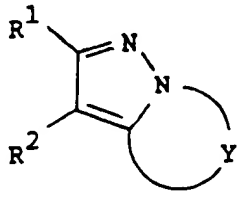
(54) Condensed pyrazole derivatives with interleukin-1 and tumour necrosis factor inhibitory activity.

(57) 1. A compound of the formula :



wherein

R^1 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent(s),

R^2 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent(s), and

Y is a bivalent radical selected from

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This invention relates to new heterocyclic derivatives. More particularly, this invention relates to pyrazole derivatives and pharmaceutically acceptable salts thereof which have pharmacological activities, processes for preparation thereof, a pharmaceutical composition comprising the same and a use of the same.

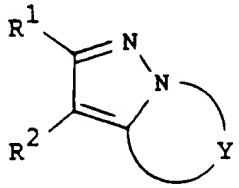
Accordingly, one object of this invention is to provide the new and useful pyrazole derivatives and pharmaceutically acceptable salts thereof which possess a strong inhibitory activity on the production of Interleukin-1 (IL-1) and a strong inhibitory activity on the production of tumor necrosis factor (TNF).

Another object of this invention is to provide processes for preparation of the pyrazole derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising said pyrazole derivatives or a pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a use of said pyrazole derivatives or a pharmaceutically acceptable salt thereof as a medicament for prophylactic and therapeutic treatment of IL-I and TNF mediated diseases such as chronic inflammatory diseases, specific autoimmune diseases, sepsis-induced organ injury, and the like in human being and animals.

The object pyrazole derivatives of the present invention are novel and can be represented by the following general formula (I)



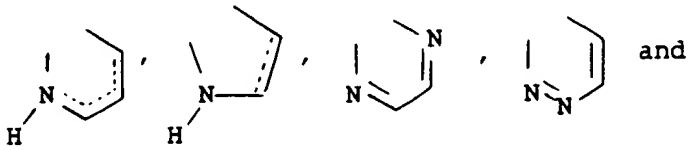
(I)

wherein

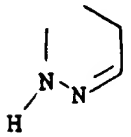
R^1 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent (s),

R^2 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent(s), and

Y is a bivalent radical selected from



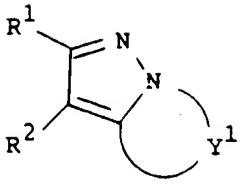
and



(in which ---- means single bond or double bond), each of which may have suitable substituent-(s).

The object compound (I) of the present invention can be prepared by the following processes.

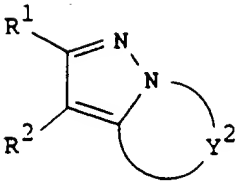
Process (2)



(Ib)

or a salt thereof

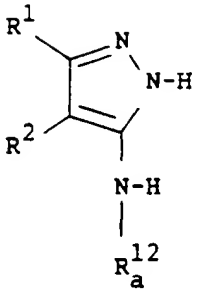
reduction



(Ic)

or a salt thereof

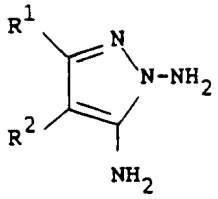
Process (3)



(II)

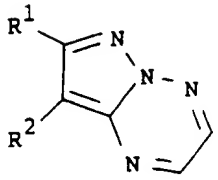
or a salt thereof

Process (5)



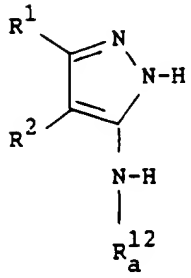
(XIIIa)
or a salt thereof

OHC-CHO
(XIV)

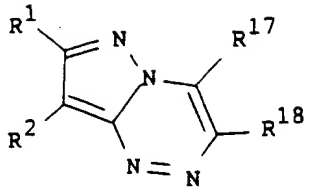


(Ig)
or a salt thereof

Process (6)



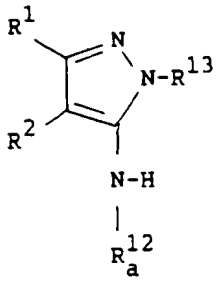
(II)
or a salt thereof



(Ii)

or a salt thereof

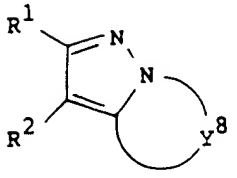
Process (8)



(XXVII)

or a salt thereof

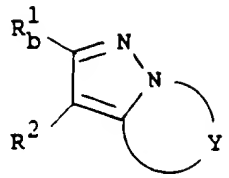
↓ cyclization



(Id)

or a salt thereof

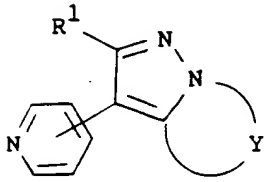
oxidation



(In)

or a salt thereof

Process (11)



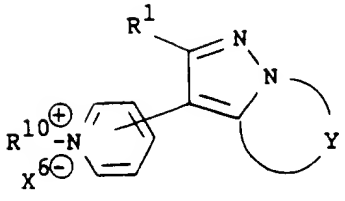
(Io)

or a salt thereof

R^{10} $-X^6$

(XX)

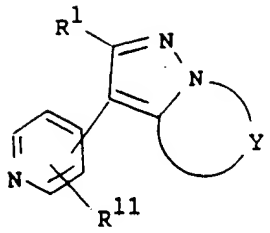
or a salt thereof



(Ip)

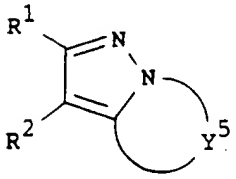
or a salt thereof

↓ oxidation



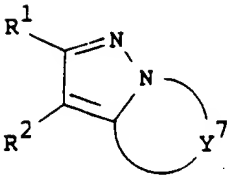
(Ir)
or a salt thereof

Process (14)



(Ik)
or a salt thereof

↓ acylation

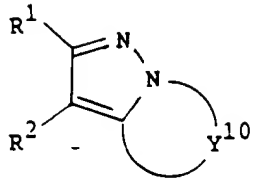


(It)
or a salt thereof

Acrylaldehyde which may have suitable substituent(s)

(XXIX)

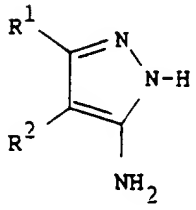
or a salt thereof



(Iv)

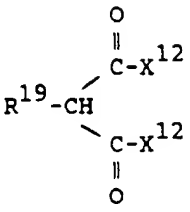
or a salt thereof

Process (17)



(IIa)

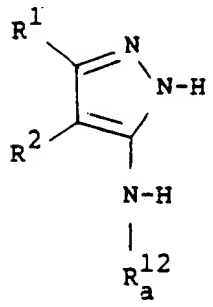
or a salt thereof



(XXX)

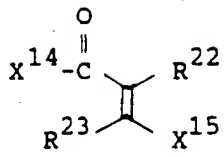
or a salt thereof

Process (19)



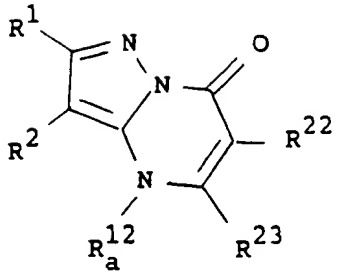
(II)

or a salt thereof



(XXXII)

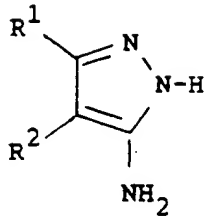
or a salt thereof



(Iy)

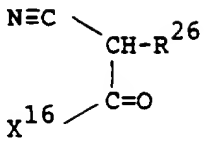
or a salt thereof

Process (21)



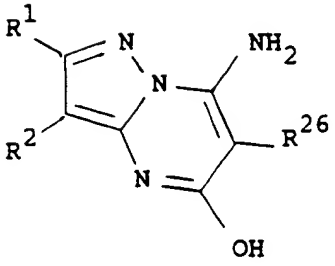
(IIa)

or a salt thereof



(XXXIV)

or a salt thereof



(Ij)

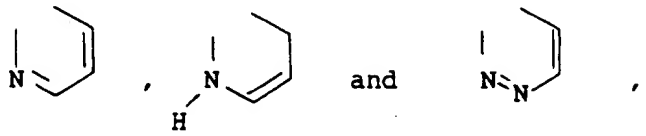
or a salt thereof

M is alkali earth metal,

X^{12}, X^{13}, X^{14}, X^{15}, X^{16} and X^{17} are each a leaving group,

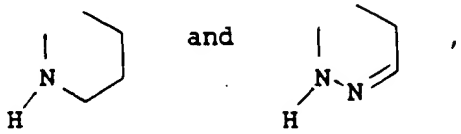
R^{13} is esterified carboxyethenyl,esterified carboxyethyl or esterified carboxyethyl, each of which may have suitable substituent(s), R^{14} is lower alkyl or aryl,

Y^1 is a bivalent radical selected from



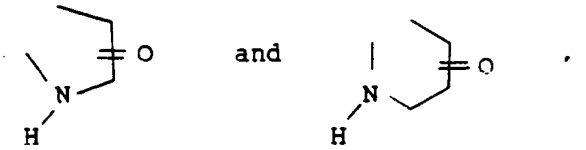
each of which may have suitable substituent(s),

Y^2 is a bivalent radical selected from



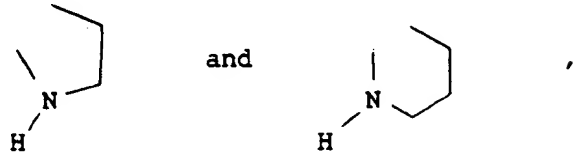
each of which may have suitable substituent(s),

Y^3 is a bivalent radical selected from



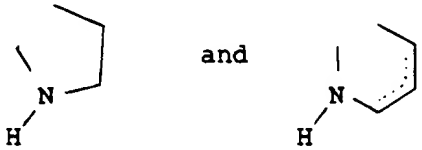
each of which may have suitable substituent(s),

Y^4 is a bivalent radical selected from



each of which may have suitable substituent(s),

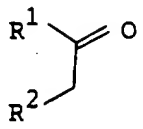
Y^5 is a bivalent radical selected from



which may have suitable substituent(s).

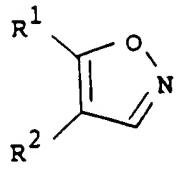
The starting compounds or salts thereof can be prepared by the following Processes.

Process (A)



(V)

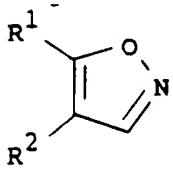
or a salt thereof



(IX)

or a salt thereof

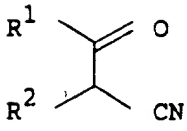
Process (C)



(IX)

or a salt thereof

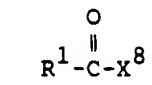
↓ Cleavage reaction of O-N bond



(X)

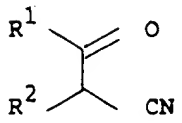
or a salt thereof

Process (E)



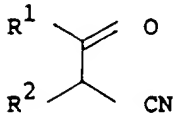
(XXII)
or a salt thereof

R^2-CH_2CN
(XXIII)
or a salt thereof



(X)
or a salt thereof

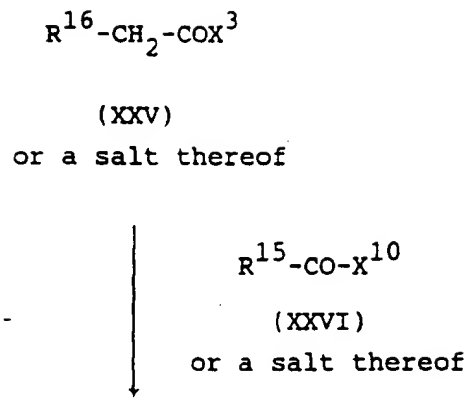
Process (F)



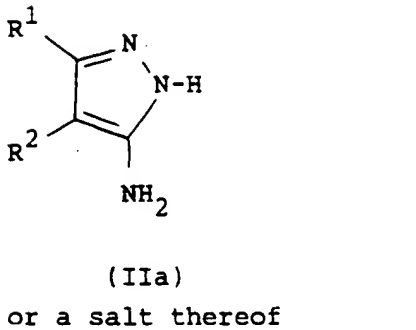
(X)
or a salt thereof

NH_2NH_2
(XII)
or a salt thereof

Process (H)



Process (I)



Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and may include e.g. a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable example and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "lower alkylthioaryl", "lower alkylsulfinylaryl" and "lower alkylsulfonylaryl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and the like, in which more preferable example may be C_1-C_4 alkyl.

Suitable "heterocyclic group" means saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be heterocyclic group such as

unsaturated 3 to 8-membered more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.,

saturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc. and the like.

Suitable "acyl" may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl.

Suitable example of said acyl may be illustrated as follows :-

Carbamoyl;

Aliphatic acyl such as lower or higher alkanoyl (e.g. formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl

2 or 3 or 4 or 5-hexynyl, etc.), mono(or di or tri)halo(lower)alkyl (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, etc.), halogen (e.g., chlorine, bromine, fluorine and iodine), carboxy, protected carboxy, hydroxy, protected hydroxy, aryl (e.g, phenyl, naphthyl, etc.), ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.), carboxy(lower)alkyl, protected carboxy(lower)alkyl, amino, protected amino, di(lower)alkylamino (e.g., dimethylamino, diethylamino, diisopropylamino, ethylmethylamino, isopropylmethylamino, ethylisopropylamino, etc.), hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, nitro, acyl as exemplified above, cyano, mercapto, lower alkylthio, (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), lower alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, etc.), lower alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, etc.), imino, and the like.

Suitable "protected carboxy" and "protected carboxy" moiety in the term "protected carboxy(lower)-alkyl" may include esterified carboxy and the like. An suitable examples of said ester moiety may be the ones such as lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, t-pentyl ester, hexyl ester, 1-cyclopropylethyl ester, etc.);
lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.);
lower alkynyl ester (e.g., ethynyl ester, propynyl ester, etc.);
lower alkoxyalkyl ester (e.g., methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.);
lower alkylthioalkyl ester (e.g., methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, isopropylthiomethyl ester, etc.);
mono(or di or tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.);
lower alkanoyloxy(lower)alkyl ester (e.g., acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 2-acetoxyethyl ester, 2-propionyloxyethyl ester, etc.);
lower alkanesulfonyl(lower)alkyl ester (e.g. mesylmethyl ester, 2-mesylethyl ester etc.);
ar(lower)alkyl ester, for example, phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.);
aryl ester which may have one or more suitable substituent(s) such as substituted or unsubstituted phenyl ester (e.g., phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, 4-chlorophenyl ester, 4-methoxyphenyl ester, etc.);
tri(lower)alkyl silyl ester;
lower alkylthioester (e.g. methylthioester, ethylthioester, etc.) and the like.

Suitable examples of ester moiety in the terms "esterified carboxyethenyl", "esterified carboxyethyl" and "esterified carboxymethyl" may be the same as exemplified above.

Suitable "protected amino" may include acylamino wherein acyl moiety can be referred to the ones as exemplified above, or the like.

Suitable "protected hydroxy" and "protected hydroxy" moiety in the term "protected hydroxy(lower)-alkyl" may include acyloxy wherein acyl moiety can be referred to the ones as exemplified above, or the like.

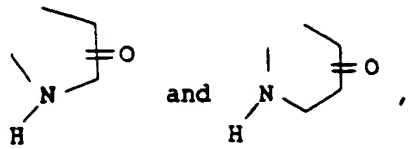
Suitable "leaving group" may include lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, etc.), aryloxy (e.g. phenoxy, naphthoxy, etc.), an acid residue or the like. Suitable "acid residue" may be halogen (e.g. chlorine, bromine, iodine, etc.), sulfonyloxy (e.g. methanesulfonyloxy, benzenesulfonyloxy, mesitylenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

Suitable "halogen" may be the same as exemplified above.

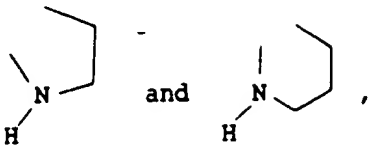
Suitable "alkali earth metal" may include magnesium, calcium, and the like.

Suitable "substituent in the definition of R^7, R^8, R^9, R_3^{12}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27} and R^{28} may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.), lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, pentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, etc.), lower alkenyl (e.g., vinyl, 1-propenyl, allyl, 1-methylallyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl, etc.), lower alkynyl (e.g., ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1 or 2 or 3-butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or 3 or 4 or 5-hexynyl, etc.), mono(or di or tri)halo(lower)alkyl (e.g. fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl,

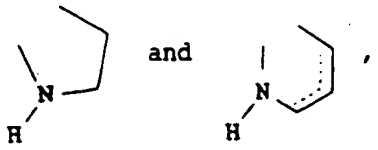
each of which may have suitable substituent(s)",
"bivalent radical selected from



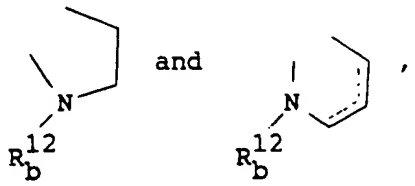
each of which may have suitable substituent(s)",
"bivalent radical selected from



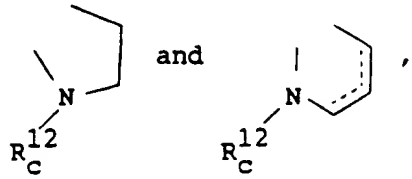
each of which may have suitable substituent(s)",
"bivalent radical selected from



each of which may have suitable substituent(s)",
"bivalent radical selected from



each of which may have suitable substituent(s)",
"bivalent radical selected from



each of which may have suitable substituent(s)",
"bivalent radical selected from

Process (2)

The compound (Ic) or a salt thereof can be prepared by subjecting the compound (Ib) or a salt thereof to reduction reaction.

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are hydrides (e.g. hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, lithium borohydride, diborane, sodium cyanoborohydride, etc.) or a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluene-sulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc) and the like.

The reaction is usually carried out in a solvent such as water, alcohol (e.g. methanol, ethanol, etc.), N,N-dimethylformamide, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely affect the reaction.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reaction is not critical and the reaction is usually carried out under cooling to heating.

Process (3)

The compound (Id) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (IV) or a salt thereof.

The reaction is usually carried out in a conventional solvent such as alcohols (e.g. methanol, ethanol, ethylene glycol, etc.), chloroform, ether, tetrahydrofuran, benzene or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, tri(lower)alkylamine, alkali metal hydride (e.g. sodium hydride, etc.), alkali metal (lower)alkoxide (e.g. sodium methoxide, sodium ethoxide, etc.), pyridine lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)-alkylbenzylamine, N,N-di(lower)alkylaniline or the like. When the base and/or the starting compound are in liquid, they can be used also as a solvent.

Process (4)

The compound (If) or a salt thereof can be prepared by subjecting the compound (Ie) or a salt thereof to reduction reaction.

This reduction can be carried out in a similar manner to that of the aforementioned Process (2), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (2).

Process (5)

The compound (Ig) or a salt thereof can be prepared by reacting the compound (XIIIa) or a salt thereof with the compound (XIV).

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylenechloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

Process (10)

The compound (In) or a salt thereof can be prepared by subjecting the compound (Im) or a salt thereof to oxidation reaction.

Oxidation is carried out in a conventional manner, which is capable of oxidizing a sulfur atom to an oxidized sulfur atom, and suitable oxidizing reagent may be oxygen acid such as periodate (e.g. sodium periodate, potassium periodate, etc.), peroxy acid such as peroxybenzoic acid (e.g., peroxybenzoic acid, m-chloroperoxybenzoic acid, etc.), and the like.

The reaction is usually carried out in a conventional solvent such as tetrahydrofuran, dioxane, dichloromethane, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (11)

The compound (Ip) or a salt thereof can be prepared by reacting the compound (Io) or a salt thereof with the compound (XX) or a salt thereof.

This reaction is usually carried out in a solvent such as benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylenechloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (12)

The compound (Iq) or a salt thereof can be prepared by reacting the compound (Ip) or a salt thereof with the compound (XXI) or a salt thereof.

This reaction is usually carried out in a solvent such as benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylenechloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (13)

The compound (Ir) or a salt thereof can be prepared by subjecting the compound (Iq) or a salt thereof to oxidation reaction.

Oxidation is carried out in a conventional manner, which is capable of oxidizing N-acyl substituted dihydropyridine to pyridine, and suitable oxidizing reagent may be sulfur, oxygen, alkali metal alkoxide, (e.g., potassium t-butoxide, etc.), or the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, t-butyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, chloroform, N,N-dimethylacetamide, N,N-dimethylformamide, decalin, tetralin or any other organic solvent which does not adversely affect the reaction.

Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

Process (14)

The compound (It) or a salt thereof can be prepared by subjecting the compound (Ik) or its reactive derivative at the imino group or a salt thereof to acylation reaction.

Suitable acylating agent to be used in the present acylation reaction may include the compound of the formula :

R_c^{12} - OH (XXXVI

(wherein R_c^{12} is acyl)

or its reactive derivative or a salt thereof.

Suitable reactive derivative at the imino group of the compound (Ik) may include a silyl derivative formed by the reaction of the compound (Ik) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide

Process (16)

The compound (Iv) or a salt thereof can be prepared by reacting the compound (IIa) or a salt thereof with the compound (XXIX) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

When the starting compound is in liquid, it can be also used as a solvent.

Process (17)

The compound (Iw) or a salt thereof can be prepared by reacting the compound (IIa) or a salt thereof with the compound (XXX) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

Process (18)

The compound (Ix) or a salt thereof can be prepared by reacting the compound (IIa) or a salt thereof with the compound (XXXI) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvent which does not adversely affect the reaction. These conventional solvent may also be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

The reaction is usually carried out in the presence of an acid including Lewis acid.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, zinc halide (e.g. zinc chloride, zinc bromide, etc.), etc.] and the like.

When the acid and/or the starting compound are in liquid, they can be also used as a solvent.

Process (19)

The compound (Iy) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (XXXII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvent which does not adversely affect the reaction. These conventional solvent may also be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

The reaction is usually carried out in the presence of an acid including Lewis acid.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, zinc halide (e.g. zinc chloride, zinc bromide, etc.), etc.] and the like.

When the acid and/or the starting compound are in liquid, they can be also used as a solvent.

Process (20)

The compound (Iz) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (XXXIII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvent which does not adversely affect the reaction. These conventional solvent may also be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

This halogenation is usually carried out by using a conventional halogenating agent such as halogen (e.g., chlorine, bromine, etc.), phosphorus trihalide (e.g., phosphorus tribromide, phosphorus trichloride, etc.), phosphorus pentahalide, (e.g., phosphorus pentachloride, phosphorus pentabromide, etc.), phosphorus oxychloride (e.g., phosphoryl trichloride, phosphoryl monochloride, etc.), thionyl halide (e.g., thionyl chloride, thionyl bromide, etc.), oxalyl halide (e.g., oxalyl chloride, oxalyl bromide, etc.) and the like.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), benzene, dioxane, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (D) - ②

The compound (IIa) or a salt thereof can be prepared by reacting the compound (XI) or a salt thereof with the compound (XII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

Process (E)

The compound (X) or a salt thereof can be prepared by reacting the compound (XXII) or a salt thereof with the compound (XXIII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvent which does not adversely affect the reaction. These conventional solvent may also be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

The reaction is usually carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g., sodium methoxide, sodium ethoxide, etc.), pyridine lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di-(lower)alkylaniline or the like.

When the base and/or the starting compound are in liquid, they can be also as a solvent.

Process (F)

The compound (IIa) or a salt thereof can be prepared by reacting the compound (X) or a salt thereof with the compound (XII) or a salt thereof.

This reaction is usually carried out in a solvent such as benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

The reaction is usually carried out in the presence of an acid including Lewis acid.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, zinc halide (e.g. zinc chloride, zing bromide, etc.), etc.] and the like.

When the acid and/or the starting compound are in liquid, they can be also as a solvent.

Process (G)

The compound (XIII) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (XXIV) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chlo-

granulamotosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease, etc.), endocrine opthalmopathy, Grave's disease, sarcoidosis, multiple scleosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), Reiter's syndrome, non infection uveitis, autoimmune keratitis (e.g. keratoconjuntivitis sicca, vernal keratoconjunctivitis, etc.), interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis {e.g. nephrotic syndrome (e.g. idiopathic nephrotic syndrome, minimal change nephropathy, etc.), etc.}, etc.), cancer cachexia, AIDS cachexia, and the like.

In order to show the utilities of the pyrazole derivatives (I) and a pharmaceutically acceptable salt thereof of the present invention, pharmacological test data of the representative compound of the pyrazole derivatives (I) are illustrated in the following.

The expression of "Example 2-(1)" in the following test means the compound prepared in Example 2-(1).

(a) Inhibitory activity on the production of Interleukin-1 (IL-1)

1. Test method

Purified human peripheral blood monocyte were stimulated with bacterial lipopolysaccharide (1 $\mu g/10^4$ cells) in the absence or presence of appropriately diluted test compound for 2 days at 37 °C in a humidified 5% CO_2 atmosphere. Culture supernatants were tested for IL-1 ELISA assay.

Test compound was dissolved in absolute DMSO (dimethyl sulfoxide) to achieve 10 mM stock solutions and was subsequently diluted in serum free RPMI1640.

IL-1 levels were quantified by a commercial ELISA kit (Ohtsuka assay, Japan) using a sandwich technique. The sensitivity levels for the detection of IL-1β were 20 pg/ml.

The inhibitory concentration that caused a 50% inhibition (IC_{50}) was calculated by regression analysis of the dose-response data.

2. Test result

Test compound	IC_{50} (M)
Example 2-(1)	3.8×10^{-8}

(b) Inhibitory activity on the production of tumor necrosis factor (TNF)

1. Test method

Purified human peripheral blood monocyte were stimulated with bacterial lipopolysaccharide (1 $\mu g/10^4$ cells) in the absence or presence of appropriately diluted test compound for 2 days at 37 °C in a humidified 5% CO_2 atmosphere. Culture supernatants were tested for TNF ELISA assay.

TNF levels were quantified by a commercial ELISA kit (Endogen, Inc. USA) using a sandwich technique. The sensitivity levels for the detection of TNF were 12 pg/ml.

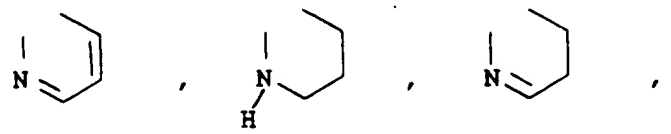
The inhibitory concentration that caused a 50% inhibition (IC_{50}) was calculated by regression analysis of the dose-response data.

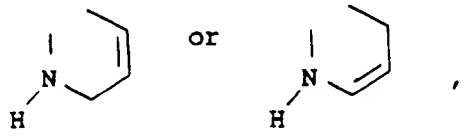
2. Test result

Test compound	IC_{50} (M)
Example 2-(1)	1.16×10^{-7}

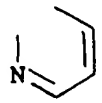
For therapeutic administration, the object compounds (I) of the present invention and pharmaceutically acceptable salts thereof are used in a form of the conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient

(in which ---- means single bond or double bond) which may have 1 to 6 (more preferably 1 to 3) substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl, halogen, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl, ar-(lower)alkyl, carboxy(lower)alkyl, protected carboxy(lower)alkyl, nitro, amino, protected amino, di(lower)-alkylamino, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, acyl, cyano, mercapto, lower alkylthio, imino and oxo [more preferably

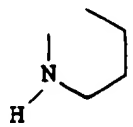




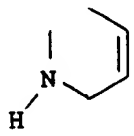
each of which may have 1 to 3 substituent(s) selected from the group consisting of phenyl, amino, acylamino, hydroxy, acyloxy, cyano, lower alkyl, lower alkanoyl, oxo, carboxy and lower alkoxycarbonyl; most preferably



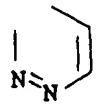
which may have one or two substituent(s) selected from the group consisting of phenyl, amino, acylamino, hydroxy, acyloxy and cyano,



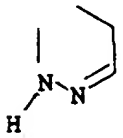
which may have one or two substituent(s) selected from the group consisting of lower alkyl, lower alkanoyl, lower alkoxycarbonyl and oxo,



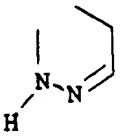
which may have oxo,



which may have one or two substituent(s) selected from the group consisting of lower alkyl and phenyl] and



which may have 1 to 4 (more preferably one or two) substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl, halogen, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl, ar(lower)alkyl, carboxy(lower)alkyl, protected carboxy-(lower)alkyl, nitro, amino, protected amino, di(lower)alkylamino, hydroxy(lower)alkyl, protected hydroxy-(lower)alkyl, acyl, cyano, mercapto, lower alkylthio, imino and oxo [more preferably



which may have lower alkyl].

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

A mixture of 1-(4-fluorophenyl)-2-(pyridin-4-yl)-ethan-1-one (5.12 g) and N,N-dimethylformamide dimethyl acetal (16 ml) was stirred at 100°C for 3 hours under nitrogen. The cooled mixture was concentrated in vacuo. The residue was crystallized from isopropyl ether to yield 3-dimethylamino-1-(4-fluorophenyl)-2-(pyridin-4-yl)-2-propen-1-one (6.15 g).

NMR ($CDCl_3$, δ) : 2.82 (6H, s), 6.99 (2H, t, J = 9Hz), 7.03 (2H, d, J = 6Hz), 7.35-7.55 (3H, m), 8.48 (2H, br)

Preparation 2

A mixture of 3-dimethylamino-1-(4-fluorophenyl)-2-(pyridin-4-yl)-2-propen-1-one (6.15 g) and hydroxylamine hydrochloride (4.75 g) in dry ethanol (40 ml) was refluxed for 20 minutes. The mixture was cooled and concentrated in vacuo. The residue was dissolved in dilute hydrochloric acid and then treated with an aqueous saturated sodium bicarbonate solution. The precipitates were collected by filtration, washed with water, and dried to give 5-(4-fluorophenyl)-4-(pyridin-4-yl)isoxazole (5.35 g).

mp : 95-97°C

NMR ($CDCl_3$, δ) : 7.15 (2H, t, J = 9Hz), 7.37 (2H, d, J = 6Hz), 7.61 (2H, dd, J = 5Hz and 9Hz), 8.46 (1H, s), 8.67 (2H, d, J = 6Hz)

Preparation 3

The following compound was obtained according to similar manners to those of Preparation 1 and Preparation 2.

5-(4-Fluorophenyl)-4-(pyrimidin-4-yl)isoxazole

mp : 125-126°C

NMR ($CDCl_3$, δ) : 7.22 (2H, t, J = 9Hz), 7.40 (1H, d, J = 5Hz), 7.83 (2H, dd, J = 5Hz and 9Hz), 8.69 (1H

NMR ($CDCl_3$, δ) : 2.52 (3H, s), 7.27 (2H, d, J = 9Hz), 7.32 (2H, d, J = 6Hz), 7.53 (2H, d, J = 9Hz), 8.40 (1H, s), 8.64 (2H, d, J = 6Hz)

(2) 5-(4-Fluorophenyl)-4-(2-fluoropyridin-4-yl)isoxazole

mp : 111-112 °C

NMR ($CDCl_3$, δ) : 6.95 (1H, s), 7.16 (2H, t, J = 9Hz), 7.19 (1H, d, J = 6Hz), 7.62 (2H, dd, J = 5Hz, 9Hz), 8.27 (1H, d, J = 6Hz), 8.45 (1H, s)

(3) 5-(4-Fluorophenyl)-4-(pyridin-2-yl)isoxazole

NMR ($CDCl_3$, δ) : 7.15 (2H, t, J = 9Hz), 7.27 (1H, t, J = 7Hz), 7.49 (1H, d, J = 7Hz), 7.69 (1H, t, J = 7Hz), 7.78 (2H, dd, J = 5Hz, 9Hz), 8.67 (1H, s), 8.69 (1H, d, J = 7Hz)

Preparation 9

The following compounds were obtained according to a similar manner to that of Preparation 4-(1).

(1) 3-(4-Methylthiophenyl)-3-oxo-2-(pyridin-4-yl)propanenitrile

mp : 234-235 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 2.49 (3H, s), 7.21 (2H, d, J = 9Hz), 7.62 (2H, d, J = 9Hz), 7.80 (2H, d, J = 6Hz), 8.15 (2H, d, J = 6Hz)

(2) 3-(4-Fluorophenyl)-2-(2-fluoropyridin-4-yl)-3-oxopropanenitrile

mp : 131-136 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 7.18 (2H, t, J = 9Hz), 7.52-7.74 (4H, m), 8.00 (1H, d, J = 6Hz)

(3) 3-(4-Fluorophenyl)-2-(3-methylpyridin-4-yl)-3-oxopropanenitrile

mp : 151-153 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 2.40 (3H, s), 7.08 (2H, t, J = 9Hz), 7.71 (2H, dd, J = 5Hz, 9Hz), 7.88 (1H, d, J = 6Hz), 7.90 (1H, s), 8.19 (1H, d, J = 6Hz)

(4) 3-(4-Fluorophenyl)-3-oxo-2-(pyridin-2-yl)propanenitrile

mp : 203-205 °C

NMR ($CDCl_3$, δ) : 7.00-7.20 (3H, m), 7.62 (1H, d, J = 8Hz), 7.80-8.05 (4H, m)

Preparation 10

The following compounds were obtained according to a similar manner to that of Preparation 5-(1).

(1) 5-Amino-3-(4-fluorophenyl)-4-(2-fluoropyridin-4-yl)pyrazole

mp : 237-239 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 6.89 (1H, br s), 7.03-7.18 (3H, m), 7.38 (2H, dd, J = 5Hz, 9Hz), 8.05 (1H, d, J = 6Hz)

(2) 5-Amino-3-(4-fluorophenyl)-4-(3-methylpyridin-4-yl)pyrazole

mp : >250 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 2.00 (3H, s), 6.95 (2H, t, J = 9Hz), 7.10-7.30 (3H, m), 8.31 (1H, d, J = 6Hz), 8.39 (1H, s)

(3) 5-Amino-3-(4-fluorophenyl)-4-(pyridin-2-yl)pyrazole

mp : 151-152 °C

NMR ($CDCl_3$, δ) : 6.60-7.15 (7H, m), 7.30-7.50 (3H, m), 8.53 (1H, d, J = 5Hz)

(4) 5-Amino-3-(4-fluorophenyl)-4-(pyridin-3-yl)pyrazole

mp : 173-176 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 7.03 (2H, t, J = 9Hz), 7.20-7.40 (3H, m), 7.62 (1H, d, J = 8Hz), 8.40-8.50 (2H, m)

Preparation 11

(1) Sodium (2.48 g) was dissolved in dry ethanol (37 ml) under nitrogen atmosphere. To the solution was added 4-fluorophenylacetonitrile (11.65 g) and ethyl isonicotinate (16.41 ml) and the solution was refluxed for 3 hours. The reaction mixture was cooled and poured into water. The ethanol of the mixture was removed under reduced pressure. The resulting aqueous solution was washed with ether and neutralized with diluted hydrochloric acid. The separated solid was collected, washed with water and dried to give 2-(4-fluorophenyl)-3-oxo-3-(pyridin-4-yl)propanenitrile (16.43 g).

mp : 230-232 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 7.12 (2H, t, J = 9Hz), 7.68 (2H, d, J = 6Hz), 7.84 (2H, dd, J = 5Hz, 9Hz), 8.69 (2H, d, J = 6Hz)

Example 2

(1) A mixture of 2-(4-fluorophenyl)-3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (56 mg) and sodium borohydride (16 mg) in ethanol (2 ml) was refluxed for 2 hours, cooled, and poured into ice water. The separated oil was extracted with dichloromethane. The extract was washed with brine, dried and concentrated in vacuo. The residue was crystallized from a mixture of ethyl acetate and ethyl ether to yield 2-(4-fluorophenyl)-3-(pyridin-4-yl)-4,5,6,7-tetrahydropyrazdlo[1,5-a]pyrimidine (44 mg).

mp : 207-209 °C

NMR ($CDCl_3$, δ) : 2.27 (2H, m), 3.40 (2H, m), 4.20 (2H, t, J = 7Hz), 4.50 (1H, s), 7.02 (2H, t, J = 9Hz), 7.08 (2H, d, J = 6Hz), 7.40 (2H, dd, J = 5Hz and 9Hz), 8.46 (2H, d, J = 6Hz)

The following compound was obtained according to a similar manner to that of Example 2-(1).

(2) 2-(4-Fluorophenyl)-3-(pyrimidin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine

mp : 168-169 °C

NMR ($CDCl_3$, δ) : 2.26 (2H, m), 3.53 (2H, m), 4.18 (2H, t, J = 7Hz), 6.78 (1H, d, J = 6Hz), 7.14 (2H, t, J = 9Hz), 7.36 (1H, br s), 7.48 (2H, dd, J = 5Hz and 9Hz), 8.22 (1H, br s), 8.94 (1H, s)

Example 3

To a suspension of sodium hydride (288 mg) in N,N-dimethylformamide (20 ml) was added dropwise a solution of 5-amino-3-(4-fluorophenyl)-4-(pyridin-4-yl)pyrazole (1.524 g) in N,N-dimethylformamide (5 ml) with ice cooling. The mixture was stirred for 30 minutes and to the mixture was added a solution of ethyl chloroacetate (883 mg) in N,N-dimethylformamide (5 ml). After stirring of the mixture for 1 hour at ambient temperature, the reaction mixture was poured into water and the separated oil was extracted with dichloromethane. The extract was washed with brine, dried and concentrated in vacuo. The residue was dissolved in a solution of sodium (138 mg) in ethanol (5 ml) and the solution was refluxed for 1 hour. The reaction mixture was cooled, poured into water and neutralized with diluted hydrochloric acid. The separated oil was extracted with dichloromethane and the extract was washed with brine, dried and concentrated in vacuo. The residue was crystallized from ethanol to yield 2,3-dihydro-6-(4-fluorophenyl)-2-oxo-7-(pyridin-4-yl)-1H-imidazo[1,2-b]pyrazole (178 mg).

mp : >250 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 4.70 (2H, s), 7.09 (2H, t, J = 9.0Hz), 7.12 (2H, d, J = 6.0Hz), 7.41 (2H, dd, J = 5.0Hz and 9Hz), 8.40 (2H, d, J = 6Hz)

Example 4

A mixture of 2,3-dihydro-6-(4-fluorophenyl)-2-oxo-7-(pyridin-4-yl)-1H-imidazo[1,2-b]pyrazole (50 mg) and diborane (0.34 mmol) in anhydrous tetrahydrofuran (5 ml) was refluxed under nitrogen atmosphere for 5 hours. After cooling of the reaction mixture, to the mixture was added 1N-hydrochloric acid (2 ml). The mixture was stirred at 60 °C for 30 minutes, cooled and neutralized with an aqueous saturated sodium bicarbonate solution. The separated oil was extracted with dichloromethane and the extract was washed with brine, dried and concentrated in vacuo. The residue was purified by thin layer chromatography on silica gel and the obtained crude solid was recrystallized from a mixture of diisopropyl ether and dichloromethane to yield 2,3-dihydro-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1H-imidazo[1,2-b]pyrazole (14 mg).

mp : 213-214 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 4.05-4.19 (2H, m), 4.24-4.39 (2H, m), 7.02 (2H, d, J = 6.0Hz), 7.05 (2H, t, J = 9.0Hz), 7.46 (2H, dd, J = 5.0Hz and 9.0Hz), 8.42 (2H, d, J = 6.0Hz)

Example 5

To a suspension of 2-(4-fluorophenyl)-3-(pyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine (100 mg) in methanol (2 ml) was added 10% methanolic hydrogen chloride (0.5 ml). The resulting clear solution was concentrated in vacuo. To the residue was added ethanol (3 ml) and the solution was concentrated in vacuo. The residue was crystallized from a mixture of ethanol and diethyl ether to give 2-(4-fluorophenyl)-3-(pyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine dihydrochloride (100 mg).

mp : >250 °C

NMR (CD_3OD, δ) : 2.30 (2H, m), 3.53 (2H, t, J = 6Hz), 4.28 (2H, t, J = 6Hz), 7.27 (2H, t, J = 9Hz), 7.51 (2H, dd, J = 6Hz, 9Hz), 7.77 (2H, d, J = 6Hz), 8.65 (2H, d, J = 6Hz)

NMR ($CDCl_3$, δ) : 2.23 (2H, m), 3.48 (2H, t, J = 6Hz), 4.18 (2H, t, J = 6Hz), 6.85-6.95 (2H, m), 7.00-7.15 (3H, m), 7.37 (1H, t, J = 7Hz), 7.51 (2H, dd, J = 5Hz, 9Hz), 8.46 (1H, d, J = 5Hz)

(7) 2-(4-Fluorophenyl)-3-(pyridin-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine

mp : 115-118 °C

NMR ($CDCl_3$, δ) : 2.25 (2H, m), 3.37 (2H, t, J = 6Hz), 4.21 (2H, t, J = 6Hz), 4.35 (1H, s), 6.98 (2H, t, J = 9Hz), 7.22 (1H, dd, J = 5Hz, 7Hz), 7.30-7.50 (3H, m), 8.40 (1H, d, J = 5Hz), 8.52 (1H, s)

Example 8

The following compound was obtained according to a similar manner to that of Example 4.

2-(4-Fluorophenyl)-4-methyl-3-(pyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine

mp : 126-128 °C

NMR ($CDCl_3$, δ) : 2.14-2.38 (2H, m), 2.62 (3H, s), 3.21 (2H, t, J = 6Hz), 4.19 (2H, t, J = 6Hz), 6.97 (2H, t, J = 9Hz), 7.15-7.30 (4H, m), 8.49 (2H, d, J = 6Hz)

Example 9

To a solution of 5-amino-4-(4-fluorophenyl)-3-(pyridin-4-yl)pyrazole (1.674 g) in ethanol (33 ml) was added O-mesitylsulfonylhydroxylamine (2.362 g). The mixture was stirred at ambient temperature for 30 minutes and to the mixture was added a solution of glyoxal in water (40%, 955 mg). The mixture was refluxed for 4 hours and cooled. The reaction mixture was poured into an aqueous saturated sodium bicarbonate solution and the separated oil was extracted with dichloromethane. The extract was washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from ethanol to give 8-(4-fluorophenyl)-7-(pyridin-4-yl)pyrazolo[1,5-b]-[1,2,4]triazine (63 mg).

mp : 177-178.5 °C

NMR ($CDCl_3$, δ) : 7.19 (2H, t, J = 9Hz), 7.55-7.70 (4H, m), 8.59 (1H, d, J = 5Hz), 8.68 (2H, br), 8.91 (1H, d, J = 5Hz)

Example 10

A mixture of sodium (28 mg), ethyl acetate (0.12 ml) and ethyl formate (0.10 ml) in dry toluene (0.5 ml) was stirred at ambient temperature for 14 hours under nitrogen. To the mixture was added 5-amino-4-(4-fluorophenyl)-3-(pyridin-4-yl)pyrazole (150 mg) in dry ethanol (1.5 ml) and the mixture was refluxed for 7 hours. The reaction mixture was cooled and the separated solid was collected and dried. The solid was dissolved in water (15 ml) and the solution was washed with ether. The aqueous solution was neutralized with diluted hydrochloric acid. The separated solid was collected, washed with water and dried to give 4,5-dihydro-3-(4-fluorophenyl)-5-oxo-2-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (62 mg).

mp : 298-299 °C

NMR ($CDCl_3$ + CD_3OD, δ) : 5.83 (1H, d, J = 7Hz), 7.25-7.50 (6H, m), 7.82 (1H, d, J = 7Hz), 8.58 (2H, br)

Example 11

(1) To a mixture of 5-amino-4-(4-fluorophenyl)-3-(pyridin-4-yl)pyrazole (100 mg) and concentrated hydrochloric acid (0.2 ml) in water (0.4 ml) was added sodium nitrite (28 mg) in water (0.12 ml) under ice cooling. The mixture was stirred for 30 minutes and to the mixture were added cold dichloromethane (5 ml), an aqueous saturated sodium bicarbonate (2 ml) solution and 1-(triphenylphosphoranylidene)-2-propanone (126 mg) in dichloromethane (2 ml). The mixture was stirred at 10 °C for 2 hours. The organic layer was separated, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 8-(4-fluorophenyl)-4-methyl-7-(pyridin-4-yl)pyrazolo[5,1-c][1,2,4]triazine (41 mg).

mp : 202.5-204.0 °C

NMR ($CDCl_3$, δ) : 2.91 (3H, s), 7.18 (2H, t, J = 9Hz), 7.62 (2H, dd, J = 5Hz, 9Hz), 7.68 (2H, d, J = 6Hz), 8.70 (2H, d, J = 6Hz), 8.79 (1H, s)

The following compound was obtained according to a similar manner to that of Example 11-(1).

(2) 8-(4-Fluorophenyl)-4-phenyl-7-(pyridin-4-yl)pyrazolo[5,1-c][1,2,4]triazine

mp : 275-276.5 °C

Example 16

To a solution of 2-(4-fluorophenyl)-3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (480 mg) in dry tetrahydrofuran (15 ml) was added acetyl chloride (0.89 ml) dropwise under ice cooling. The mixture was stirred at ambient temperature for 1 hour and to the mixture was added a solution of methyl magnesium bromide in tetrahydrofuran (1 mole solution, 12.42 ml) under ice cooling. The mixture was stirred at ambient temperature for 2 hours and to the mixture was added an aqueous saturated sodium bicarbonate solution. The separated oil was extracted with dichloromethane and the solution was washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 3-(1-acetyl-1,2-dihydro-2-methylpyridin-4-yl)-2-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine (327 mg).

NMR ($CDCl_3$, δ) : 1.26 (3H, d, J = 7Hz), 2.21 (3H, s), 5.24-5.40 (1H, m), 5.47 (1H, d, J = 7Hz), 5.82 (1H, d, J = 6Hz), 6.52 (1H, d, J = 7Hz), 6.86 (1H, dd, J = 4Hz, 7Hz), 7.15 (2H, t, J = 9Hz), 7.78 (2H, dd, J = 5Hz, 9Hz), 8.51 (1H, d, J = 4Hz), 8.67 (1H, d, J = 7Hz)

Example 17

A mixture of 3-(1-acetyl-1,2-dihydro-2-methylpyridin-4-yl)-2-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine (315 mg) and sulfur (146 mg) in decaline (3 ml) was stirred at 190 °C for 2 hours. The reaction mixture was cooled and purified by column chromatography on silica gel to give 2-(4-fluorophenyl)-3-(2-methylpyridin-4-yl)pyrazolo[1,5-a]pyrimidine (135 mg) as crystals.

mp : 164-166 °C

NMR ($CDCl_3$, δ) : 2.59 (3H, s), 6.95 (1H, dd, J = 4Hz, 7Hz), 7.11 (2H, t, J = 9Hz), 7.26 (1H, d, J = 5Hz), 7.42 (1H, s), 7.61 (2H, dd, J = 5Hz, 9Hz), 8.48 (1H, d, J = 5Hz), 8.59 (1H, d, J = 5Hz), 8.73 (1H, d, J = 7Hz)

Example 18

A mixture of 3-(4-fluorophenyl)-2-(pyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine (100 mg), triethylamine (0.4 ml) and acetic anhydride (0.2 ml) in dry 1,2-dichloroethane (3 ml) was refluxed for 2 days. The reaction mixture was cooled and concentrated in vacuo. The residue was dissolved in dichloromethane and the solution was washed with an aqueous saturated sodium bicarbonate solution and brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 4-acetyl-3-(4-fluorophenyl)-2-(pyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine (60 mg).

mp : 184-185 °C

NMR ($CDCl_3$, δ) : 1.60 (s), 2.28 (2H, m), 4.01 (2H, t, J = 6Hz), 4.36 (2H, t, J = 6Hz), 7.00-7.25 (4H, m), 7.33 (2H, d, J = 5Hz), 8.52 (2H, d, J = 5Hz)

Example 19

A mixture of 8-(4-fluorophenyl)-4-methyl-7-(pyridin-4-yl)pyrazolo[5,1-c][1,2,4]triazine (53 mg) and sodium borohydride (13 mg) in ethanol (1 ml) was refluxed for 3 hours, cooled and poured into ice-water. The separated oil was extracted with dichloromethane. The extract was washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 1,4-dihydro-8-(4-fluorophenyl)-4-methyl-7 (pyridin-4-yl)-pyrazolo[5,1-c][1,2,4]triazine (13 mg).

mp : 203.5-204.5 °C

NMR ($CDCl_3$, δ) : 1.75 (3H, d, J = 7Hz), 5.02 (1H, dq, J = 2Hz, 7Hz), 6.78 (1H, d, J = 2Hz), 7.11 (2H, t, J = 9Hz), 7.20 (2H, dd, J = 5Hz, 9Hz), 7.40 (2H, d, J = 6Hz), 7.84 (1H, s), 8.50 (2H, d, J = 6Hz)

Example 20

2-(4-Fluorophenyl)-3-(pyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine dihydrochloride (183 mg) was dissolved in hot aqueous isopropyl alcohol solution (5.5 ml). The solution was cooled and the separated solid was collected, washed with isopropyl alcohol and dried to give 2-(4-fluorophenyl)-3-(pyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine hydrochloride (82 mg).

mp : >250 °C

IR (Nujol) : 3300, 2550, 2040, 1955, 1855, 1625 cm^{-1}

Example 26

A mixture of 5-amino-3-(4-fluorophenyl)-4-(pyridin-4-yl)pyrazole (100 mg) and 1,1-dicyano-2-ethoxyethylene (49 mg) in acetic acid (2 ml) was refluxed for 1 hour. The reaction mixture was concentrated in vacuo and the residue was crystallized from ethanol to give 7-amino-6-cyano-2-(4-fluorophenyl)-3-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidine (77 mg).

mp : >280°C

NMR (DMSO-d_6, δ) : 7.35 (2H, t, J=9Hz), 7.45 (2H, d, J=6Hz), 7.65 (2H, dd, J=6.9Hz), 8.50 (1H, s), 8.55 (2H, d, J=6Hz), 9.20 (2H, br s)

Example 27

A mixture of 5-amino-3-(4-fluorophenyl)-4-(pyridin-4-yl)pyrazole (100 mg), 1,2-bis-(4-fluorophenyl)-2-hydroxyethan-1-one (167 mg) and concentrated hydrochloric acid (1 ml) in ethanol was refluxed for 5 hours. The reaction mixture was concentrated in vacuo and the obtained crystalline was washed with hot ethanol to give 2,3,6-tris-(4-fluorophenyl)-7-(pyridin-4-yl)-1H-imidazo[1,2-b]pyrazole hydrochloride (50 mg).

mp : >260°C

NMR (DMSO-d_6, δ) : 7.25 (6H, m), 7.55-7.80 (8H, m), 8.55 (2H, d, J=6Hz)

Example 28

A mixture of 5-amino-3-(4-fluorophenyl)-4-(pyridin-4-yl)pyrazole (1.02 g) and 1,1-bis(ethoxycarbonyl)-2-ethoxyethylene (864 mg) in acetic acid (10 ml) was refluxed for 3 hours. After cooling, the crude crystalline was obtained and washed with ethanol to give 4,7-dihydro-6-ethoxycarbonyl-2-(4-fluorophenyl)-3-(pyridin-4-yl)-7-oxopyrazolo[1,5-a]pyrimidine (1.23 g).

mp : >250°C

Example 29

To a mixture of 4,7-dihydro-6-ethoxycarbonyl-2-(4-fluorophenyl)-3-(pyridin-4-yl)-7-oxopyrazolo[1,5-a]-pyrimidine (100 mg) in tetrahydrofuran (4 ml) was added lithium borohydride (2 mole in tetrahydrofuran, 0.26 ml) at room temperature and the mixture was refluxed for 1 hour. After cooling, the reaction mixture was quenched with an aqueous saturated ammonium chloride solution and extracted with ethyl acetate. The extracts were washed with brine, dried and concentrated in vacuo. The residue was crystallized from ethanol to give 6-ethoxycarbonyl-2-(4-fluorophenyl)-7-oxo-3-(pyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine (40 mg).

mp : >250°C (dec.)

NMR (DMSO-d_6, δ) : 1.20 (3H, t, J=7Hz), 3.70-3.95 (2H, m), 4.15-4.30 (3H, m), 7.20-7.35 (4H, m), 7.45 (2H, dd, J=6.9Hz), 8.00 (1H, br s), 8.40 (2H, d, J=6Hz)

Example 30

A mixture of 4,7-dihydro-6-ethoxycarbonyl-2-(4-fluorophenyl)-3-(pyridin-4-yl)-7-oxopyrazolo[1,5-a]-pyrimidine (946 mg) in sulfuric acid (40% in water, 5 ml) was refluxed for 2 hours. After cooling, the pH of the reaction mixture was adjusted to 5 with an aqueous saturated sodium bicarbonate solution. The crude crystalline was obtained and washed with hot ethanol to give 4,7-dihydro-6-carboxy-2-(4-fluorophenyl)-3-(pyridin-4-yl)-7-oxopyrazolo[1,5-a]pyrimidine (275 mg).

mp : 215-218°C

NMR (DMSO-d_6, δ) : 7.40 (2H, t, J=9Hz), 7.65 (2H, dd, J=6,9Hz), 8.10 (2H, d, J=6Hz), 8.60-8.70 (3H, m)

Example 31

The following compounds were obtained according to a similar manner to that of Example 11-(1).

(1) 8-(4-Fluorophenyl)-7-(pyridin-4-yl)pyrazolo[5,1-c]-[1,2,4]triazine

mp : 180-182°C

NMR ($CDCl_3$, δ) : 7.20 (2H, t, J=9Hz), 7.55-7.70 (4H, m), 8.59 (1H, d, J=5Hz), 8.70 (2H, d, J=6Hz), 8.90 (1H, d, J=5Hz)

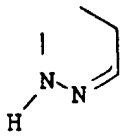
wherein

R^1 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent(s),

R^2 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent(s), and

Y is a bivalent radical selected from

and



(in which ---- means single bond or double bond), each of which may have suitable substituent(s), and

pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein

R^1 is aryl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl, halogen, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl, ar(lower)alkyl, carboxy-(lower)alkyl, protected carboxy(lower)alkyl, amino, protected amino, di(lower)alkylamino, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, nitro, acyl, cyano, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl and imino, or unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s) which may have 1 to 3 suitable substituent(s),

R^2 is aryl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl, halogen, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl, ar(lower)alkyl, carboxy-(lower)alkyl, protected carboxy(lower)alkyl, amino, protected amino, di(lower)alkylamino, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, nitro, acyl, cyano, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl and imino, or unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl, halogen, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl, ar(lower)alkyl,carboxy(lower)alkyl, protected carboxy-(lower)alkyl, amino, protected amino, di(lower)alkylamino, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, nitro, acyl, cyano, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl and imino,

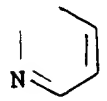
Y is a bivalent radical selected from

3. A compound of claim 2, wherein

R^1 is phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl, halogen, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl, ar(lower)alkyl, carboxy-(lower)alkyl, protected carboxy(lower)alkyl, amino, protected amino, di(lower)alkylamino, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, nitro, acyl, cyano, mercapto,lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl and imino, or unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s),

R^2 is phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl, halogen, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl,ar(lower)alkyl, carboxy(lower)-alkyl, protected carboxy(lower)alkyl, amino, protected amino, di(lower)alkylamino, hydroxy-(lower)alkyl, protected hydroxy(lower)alkyl, nitro, acyl, cyano, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl and imino, or unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) which may have 1 to 2 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, mono(or di or tri)halo(lower)alkyl, halogen, carboxy, protected carboxy, hydroxy, protected hydroxy, aryl, ar(lower)alkyl, carboxy(lower)alkyl, protected carboxy-(lower)alkyl, amino, protected amino, di(lower)alkylamino, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, nitro, lower alkanoyl, cyano, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl and imino,

Y is a bivalent radical selected from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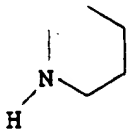
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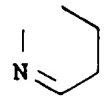
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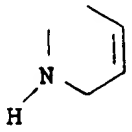
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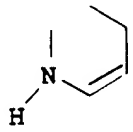
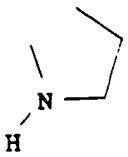

,

each of which may have 1 to 3 substituent(s) selected from the group consisting of phenyl, amino, acylamino, hydroxy, acyloxy, cyano, lower alkyl, lower alkanoyl, oxo, carboxy and lower alkoxycarbonyl;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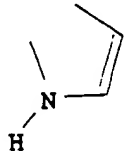
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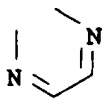
each of which may have one or two substituent(s) selected from the group consisting of oxo and phenyl which may have halogen;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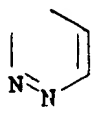
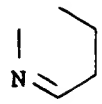
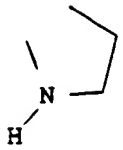
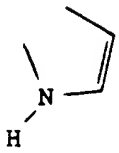




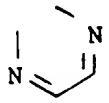
which may have 1 to 3 lower alkyl;



which may have oxo group;



which may have one or two phenyl which may have halogen;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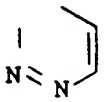
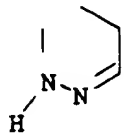
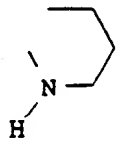


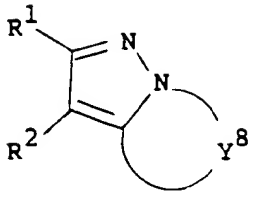
which may have one or two substituent(s) selected from the group consisting of lower alkyl and phenyl; and



which may have lower alkyl.

5. A compound of claim 4, wherein
R^1 is halophenyl,
R^2 is pyridyl and
Y is

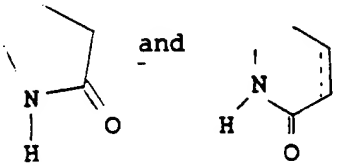




wherein

R^1 and R^2 are each as defined above and

Y^8 is a bivalent radical selected from

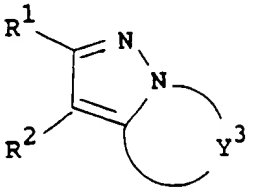


(in which ----is as defined above),

each of which may have suitable substituent(s),

or a salt thereof, or

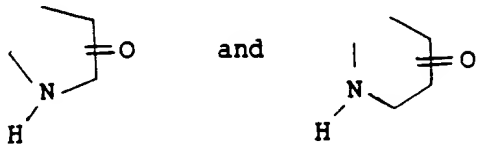
(4) subjecting a compound of the formula :



wherein

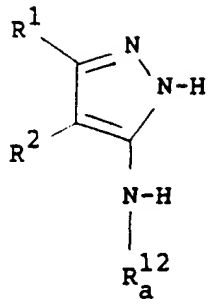
R^1 and R^2 are each as defined above and

Y^3 is a bivalent radical selected from

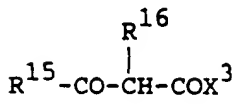


each of which may have suitable substituent(s),

or a salt thereof to reduction reaction to give a compound of the formula :



wherein R^1, R^2 and R_a^{12} are each as defined above, or a salt thereof with a compound of the formula :

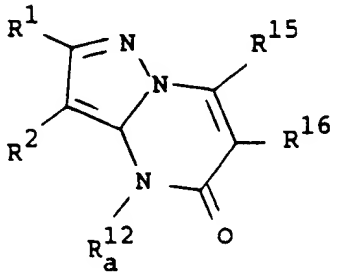


wherein

R^{15} and R^{16} are each hydrogen or substituent and

X^3 is a leaving group,

or a salt thereof to give a compound of the formula :

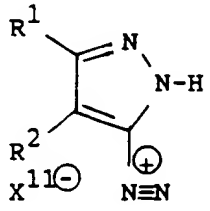


wherein

R^1, R^2 R_a^{12} , R^{15} and R^{16} are each as defined above,

or a salt thereof, or

(7) reacting a compound of the formula :

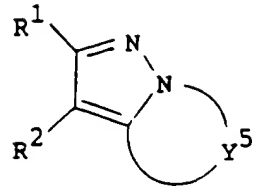


wherein

R^1 and R^2 are each as defined above and

X^{11} is an acid residue,

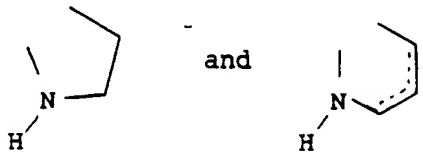
or a salt thereof with a compoound of the formula :



wherein

R^1 and R^2 are each as defined above and

Y^5 is a bivalent radical selected from



(in which ---- is as defined above), each of which may have an oxo group, or a salt thereof with a compound of the formula :

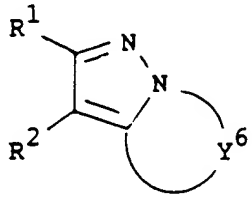
$R_b^{12} - X^5$

wherein

R_b^{12} is lower alkyl and

X^5 is a leaving group,

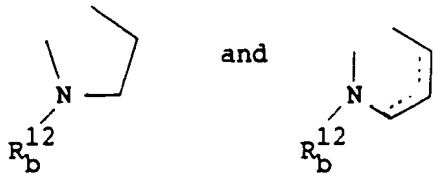
or a salt thereof to give a compound of the formula :



wherein

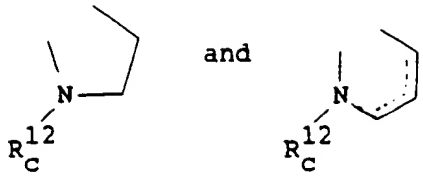
R^1 and R^2 are each as defined above and

Y^6 is a bivalent radical selected from

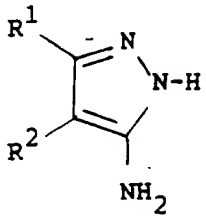


(in which R_b^{12} and ---- are each as defined above),

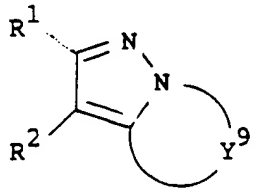
each of which may have an oxo group.



(in which ---- is as defined above and R_c^{12} is acyl),
each of which may have an oxo group,
or a salt thereof, or
(15) reacting a compound of the formula :

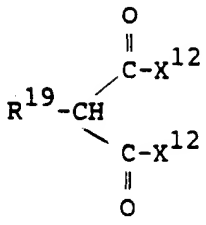


wherein
R^1 and R^2 are each as defined above, or a salt thereof with propandial which may have suitable substituent(s) or a salt thereof to give a compound of the formula :

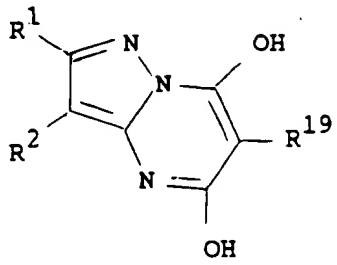


wherein
R^1 and R^2 are each as defined above and
Y^9 is

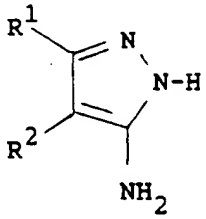
which may have suitable substituent(s),
or a salt thereof, or
(16) reacting a compound of the formula :



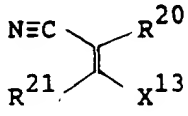
wherein
R^{19} is hydrogen or substituent and
X^{12} is a leaving group,
or a salt thereof to give a compound of the formula :



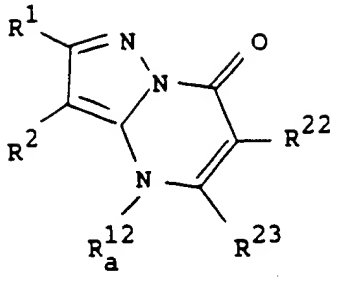
wherein
R^1, R^2 and R^{19} are each as defined above,
or a salt thereof, or
(18) reacting a compound of the formula :



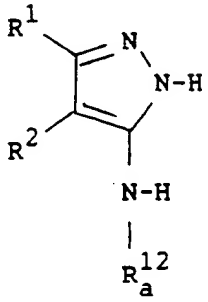
wherein
R^1 and R^2 are each as defined above,
or a salt thereof with a compound of the formula :



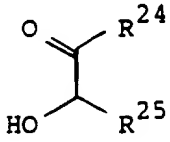
wherein
R^{20} and R^{21} are each hydrogen or substituent and
X^{13} is a leaving group,
or a salt thereof to give a compound of the formula :



wherein
R^1, R^2, R^{22}, R^{23} and R_a^{12} are each as defined above,
or a salt thereof, or
(20) reacting a compound of the formula :

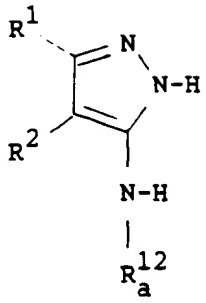


wherein
R^1, R^2 and R_a^{12} are each as defined above,
or a salt thereof with a compound of the formula :

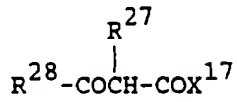


wherein
R^{24} and R^{25} are each hydrogen or substituent,
or a salt thereof to give a compound of the formula :

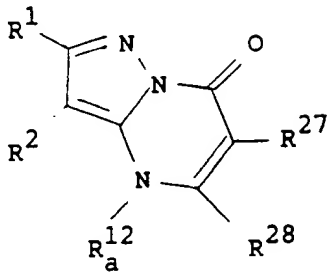
or a salt thereof, or
(22) reacting a compound of the formula :



wherein
R^1, R^2 and R_a^{12} are each as defined above,
or a salt thereof with a compound of the formula :



wherein
R^{27} and R^{28} are each hydrogen or substituent and
X^{17} is a leaving group,
or a salt thereof to give a compound of the formula :



wherein
R^1, R^2, R^{27}, R^{28} and R_a^{12} are each as defined above,
or a salt thereof.

8. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

9. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as an inhibitor on the production of Interleukin-1 (IL-1) and an inhibitor on the production of tumor necrosis factor (TNF).

10. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for manufacture of medicament for the prophylactic or therapeutic treatment of Interleukin-1 (IL-1) and tumor necrosis factor (TNF) mediated diseases.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 531 901 A3**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **92115154.4**

(22) Date of filing: **02.09.92**

(51) Int. Cl.5: **C07D 487/04**, A61K 31/505, A61K 31/53, A61K 31/415, ///(C07D487/04,239:00,231:00), (C07D487/04,235:00,231:00), (C07D487/04,253:00,231:00)

(30) Priority: **09.09.91 GB 9119267**
02.03.92 GB 9204464

(43) Date of publication of application:
17.03.93 Bulletin 93/11

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(88) Date of deferred publication of the search report:
05.05.93 Bulletin 93/18

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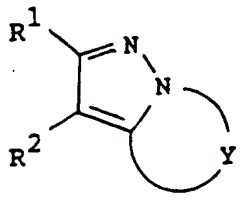
(54) **Condensed pyrazole derivatives with interleukin-1 and tumour necrosis factor inhibitory activity.**

(57) 1. A compound of the formula :



wherein
R^1 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable substituent(s),
R^2 is aryl which may have suitable substituent(s) or heterocyclic group which may have suitable

EP 0 531 901 A3

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EUROPEAN SEARCH REPORT

Application Number

EP 92 11 5154.4

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 353 047 (SANKYO) * claim 1; page 2, lines 22,23; page 10, compound 26 and page 12, compound 59 *	1,8	C07D487/04 A61K31/505 A61K31/53 A61K31/415
X	CANADIAN JOURNAL OF CHEMISTRY vol. 59, no. 19, 1981, OTTAWA CA pages 2826 - 2832 C. BELLEC ET AL. 'Deaminative electrochemical reduction of pyrazolo(1,5-a)pyrimidine-7-amines' * page 2827, table I, compound 1f; page 2828, table II, compound 2f; page 2829, table III, compound 3f *	1	//(C07D487/04, 239:00,231:00) (C07D487/04, 235:00,231:00) (C07D487/04, 253:00,231:00)
X	SYNTHESIS 1977, STUTTGART DE pages 556 - 559 G. EGE ET AL. 'Cycloaddition von Ynaminen an Diazo-azole. Ein neuer Zugang zu Azolo(5,1-c)(1,2,4)triazinen' * page 556, table 3, compounds 4du, 4dv, 4dw *	1	
A	WO-A-9 100 092 (SMITH KLINE BEECHAM) * claims 1,22 *	1,8	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07D A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	08 MARCH 1993	ALFARO FAUS I.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)